'Old drugs for new applications': can orthopedic research benefit from this strategy?

Ther Adv Musculoskel Dis
(2011) 3(4) 201–205
DOI: 10.1177/1759720X11408487

Xiaohua Pan*, Wenxiang Cheng*, Jiali Wang, Ling Qin, Yuxiao Lai, Jian Tang, Peng Shang, Peigen Ren and Peng Zhang

***Abstract*:** New drug exploration is difficult in a clinical setting and the development of new drugs may be costly and time consuming. With further research into the pathological mechanisms and etiology of diseases as well as the rapid development of biological techniques, many '*old drugs*' that have been applied in clinics may have new therapeutic functions which may shed light on clinical management. Based on this, we have investigated the '*old drugs for new applications*' strategy in pharmacology which may be less expensive and more efficient in the clinical setting. In this paper we have explored and illustrated the potential applications of '*old drugs*' for the treatment of orthopedic diseases, especially in arthritis and osteoporosis therapy.

***Keywords*:** cholinergic anti-inflammatory pathway, cholinergic antinociceptive pathway, old drugs for new applications, orthopedic research, rheumatoid arthritis

Introduction

It has been reported that to introduce a new drug to the market can cost an average of US$897 million and can also be a very time-consuming process (it may take more than 15 years before a drug receives approval) [Dickson and Gagnon, 2004]. Moreover, some newly discovered drugs in developmental stage are unable to receive US Food and Drug Administration (FDA) approval due to undesirable adverse reactions or even toxicity. Therefore, it is often helpful to explore new indications for already-existing drugs with known adverse drug reactions, an approach that is commonly called '*old drugs for new applications*'.

Many orthopedic diseases such as rheumatoid arthritis (RA), osteoporosis, etc., have become endemic with the trend of an aging population, and the treatment of these diseases can entail enormous expense. The discovery of cheap and efficient drugs is the ultimate goal of pharmacologists and clinicians. With this in mind, it is reasonable to believe that the '*old drugs for new applications*' strategy will decrease the therapeutic cost for patients and may herald a new era for drug research and development.

The current status of *'old drugs for new applications'*

The *'old drugs for new applications'* is not an uncommon strategy. A well known application is that of aspirin, a typical nonsteroidal anti-inflammatory drug (NSAID) used to relieve pain and reduce inflammation [Yasuda *et al.* 2008]. Several studies have also shown a cardioprotective effect and, consequently, aspirin is now widely used in the prophylaxis and management of cardiac diseases [Sciulli *et al.* 2006; Howard and Delafontaine, 2004]. In addition, an anticancer effect has also been found and studies have shown that even at a 75 mg/day dose, aspirin may reduce colorectal cancer risk after a lag of a year or so [Benamouzig and Uzzan, 2010; Yeomans, 2010]. The application of phosphoantigens for the potential therapy of flu is another classical example which has been investigated by Qin and colleagues [Qin *et al.* 2009]. Phosphoantigens have been successfully used for decades to treat osteoporosis. However, new properties have been discovered recently. Phosphoantigens can also enhance the function and increase the number of γδ T cells (gamma delta T cells) in the body thus boosting the immune response to influenza and limiting viral

Correspondence to:
Peng Zhang,
Center for Translational Medicine Research and Development, Shenzhen Institutes of Advanced Technology, Chinese Academy of Sciences, Shenzhen, Guangdong Province, China
superzhangpeng@sina.com

Xiaohua Pan
Department of Orthopaedics, Second Clinical Medical College, Ji'nan University, Shenzhen, Guangdong Province, China

Wenxiang Cheng
Jiali Wang
Ling Qin
Yuxiao Lai
Jian Tang
Peigen Ren
Peng Shang
Center for Translational Medicine Research and Development, Shenzhen Institutes of Advanced Technology, Chinese Academy of Sciences, Shenzhen, Guangdong Province, China

*These two authors contributed equally and should both be considered as the first author.

production. Another example of 'new uses for old drugs' is offered by the antihypertensive drugs, angiotension-converting enzyme inhibitor (ACEI) and angiotensin receptor blocker (ARB) which have also been found to be useful agents for migraine prophylaxis [Tronvik *et al.* 2003; Schrader *et al.* 2001]. Many other clinical examples can be found to support the '*old drugs for new applications*' strategy.

'Old drugs' for the treatment of orthopedic diseases

Focusing on research into the pathological mechanism of orthopedic diseases, new indications and therapeutic roles can be found in *'old drugs'*. RA and osteoporosis will be exemplified and illustrated in detail in this paper.

RA is an autoimmune disease where the immune system attacks the lining of body's joints, which may cause swelling, stiffness, pain and can eventually damage bones, tendons and cartilage, causing deformities and limiting motion [Lindstrom and Robinson, 2010]. Inflammation plays a crucial role in the pathological process of RA and the majority of available drugs were designed to block the inflammatory process. NSAIDs and disease-modifying antirheumatic drugs (DMARDs) are commonly used and widely accepted by rheumatologists and orthopedic surgeons as the gold standard prescription in clinics [Salt and Frazier, 2010]. Since none of the available drugs can cure this disease completely, the exploration of new drugs is needed.

Cholinergic receptor agonists, such as GTS-21 (DMXB-A), that have been used for the treatment of neurological disorders [Olincy *et al.* 2006; Martin *et al.* 2004; Kem, 2000] may offer a therapeutic potential in the treatment of RA. This is as a result of the newly discovered cholinergic anti-inflammatory and antinociceptive pathway. GTS-21 acts as a partial agonist of neural nicotinic acetylcholine receptors which may bind to both the $\alpha_4\beta_2$ and α_7 subtypes [Meyer *et al.* 1997]. If we consider the role of the cholinergic receptor in the pathogenesis of RA [van Maanen *et al.* 2009] and the cholinergic anti-inflammatory pathway (first reported by Tracey [Tracey, 2002]), GTS-21 may have a role as a potential RA therapeutic agent. The cholinergic anti-inflammatory pathway indicates that the α_7 nicotinic acetylcholine receptor (α_7nAChR) represents the molecular dovetail between the cholinergic nervous system and the innate immune system [Wang *et al.* 2003]. The receptor is mainly expressed on the membrane of immune cells, including monocytes, macrophages, T and B lymphocytes, and dendritic cells [Bendixen *et al.* 2001]. The activation of α_7 nAChR inhibits, the production of pro-inflammatory cytokines (tumor necrosis factor alpha [TNF-α], interleukin [IL]-1, and IL-18) rather than anti-inflammatory cytokines [Borovikova *et al.* 2000]. This is due mainly to the activation of JaK_2-$STAT_3$ signaling transduction pathway and to the inhibition of NF-κB pathway [Altavilla *et al.* 2006; de Jonge *et al.* 2005]. In addition to the anti-inflammatory effect, an antinociceptive function of nAChRs was also found [Rowley *et al.* 2010], which may relieve pain in RA patents. Therefore, the potential application of cholinergic receptor agonists (GTS-21, etc.), which are already used by neurologist for the treatment of diseases such as Alzheimer's [Gu *et al.* 2009], for the treatment of RA [Pan *et al.* 2010a, 2010b] seems promising (Figure 1) for the treatment of RA [Pan et al.2010a, 2010b].

The potential role of statins for the treatment of osteoporosis is another good example worth mentioning. Statins are specific inhibitors of 3-hydroxy-3methyl-glutaryl coenzyme A (HMG-CoA) reductase and are some of the most used drugs in the treatment of atherosclerosis and other cardiovascular conditions [Pedersen *et al.* 1996]. Recent *in vitro* research has indicated an anabolic effect of these drugs on bone [Yazawa *et al.* 2005]. Moreover, simvastatin was found to enhance bone formation through induction of BMP-2 and alkaline phosphatase and by the accumulation of bone matrix proteins [Maeda *et al.* 2001]. The anabolic effect of statins on bone has also been supported by *in vivo* studies. Oral administration of simvastatin was found to increase the trabecular bone volume and bone formation rate with a concomitant decrease in osteoclast numbers in ovariectomized rats, as well as in rats with intact ovaries, which also minimized the ovariectomy-induced reduction in cancellous bone volume [Oxlund and Andreassen, 2004; Oxlund *et al.* 2001]. Due to to their liver specificity and very poor distribution to the periphery, the probability of statins reaching the bone microenvironment is very low [Mundy, 2001]. Therefore, it is extremely important to evaluate the potential skeletal effect of statins. Much preliminary research has been done regarding this issue. *In vivo* studies have indicated that dermal application of statins in

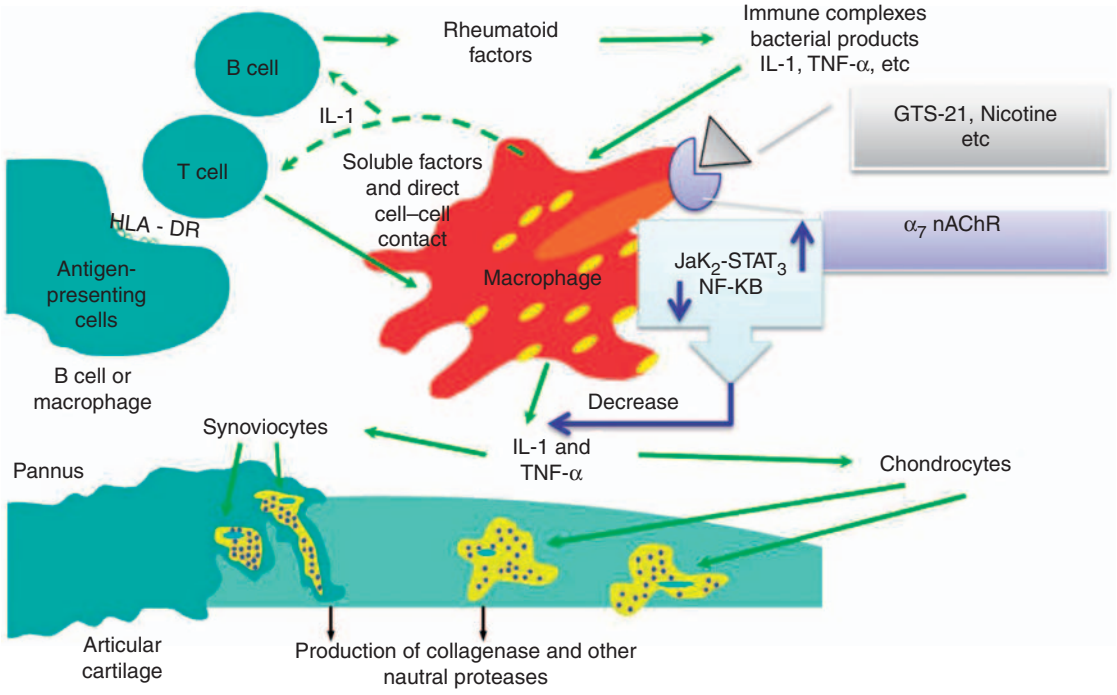

Figure 1. The diagrammatic illustration of the pathological process of rheumatoid arthritis and the potential application of cholinergic receptor agonists.

rats, compared with oral gavage administration, may have a greater effect in increasing the bone formation and plasma concentration [Gutierrez *et al.* 2006]. With the recent advances of polymer science, various biocompatible polymers have been developed which are widely used as a novel drug-delivery systems. The controlled delivery of simvastatin, to provide an example, showed a significant effect on bone formation [Thylin *et al.* 2002]. In addition to the aforementioned, other interestin drug cases can be mentioned in the orthopaedic settings. Erythromycin, which has been used as an antibiotic, has also been used to treat aseptic loosening and osteolysis in animal models [Ren *et al.* 2006] and most recently in patients [Ren *et al.* 2009; Zhang and Qin].

How to perform the *'old drugs for new applications'* strategy?

There are still several challenges to overcome to predict or identify new potential uses of '*old drugs*'. Often serendipity plays an important role in this process.

The discovery of sildenafil citrate (Viagra) is a typical example. Viagra was initially studied for its role in hypertension and angina pectoris. The results of phase I clinical trials showed only a little effect on angina but instead, it was observed a marked induction of penile erection [Boolell *et al.* 1996]. Based on this discovery, Viagra was patented in 1996 and approved for use in erectile dysfunction by the FDA on 27 March 1998. It soon became a great success. This example clearly shows how the investigation of side effects may lead to the discovery of alternative new treatment indications. However, although serendipity has an important role in research, other approaches are needed to explore new properties and uses from existing old drugs. This strategy can be very convenient as often, when a new indication is discovered, the drug has already undergone preclinical and clinical testing.

Keiser and colleagues' research have shed light on this important issue [Keiser *et al.* 2009]. Their research was based on the criteria that if a drug and a ligand have similar three-dimensional structures, then there is a good chance that the drug will bind to the same protein as the ligand. Thousands new targets for existing drugs could be identified using computer-aided molecular modelling programs by screening and comparing molecular structures of endogenous compounds with those of existing drugs.

The '*old drugs for new applications*' strategy can be divided into two stages. In the first stage, serendipity plays an important role and depends on the careful observation of researchers which may find new therapeutic indications from the side effect of the drugs. The use of modern tools and techniques is also important. As we have mentioned above, Keiser and colleagues' research should be further investigated and represents a very promising tool for the investigation of new indications for old drugs.

Future prospects

The *'old drugs for new applications'* strategy may provide cost-effective treatments especially in developing countries with limited resources and funding. In addition, as the drug has often already undergone preclinical and clinical testing this strategy will greatly reduce the cost of drugs in clinics and more patients will benefit.

Funding

This research was supported by the National Natural Science Foundation of China (grant number 81000786).

Conflict of interest statement

None declared.

References

Altavilla, D., Guarini, S., Bitto, A., Mioni, C., Giuliani, D., Bigiani, A. *et al.* (2006) Activation of the cholinergic anti-inflammatory pathway reduces NF-kappaB activation, blunts TNF-alpha production, and protects against splanchnic artery occlusion shock. *Shock* 25: 500–506.

Benamouzig, R. and Uzzan, B. (2010) Aspirin to prevent colorectal cancer: time to act? *Lancet* 376: 1713–1714.

Bendixen, A.C., Shevde, N.K., Dienger, K.M., Willson, T.M., Funk, C.D. and Pike, J.W. (2001) IL-4 inhibits osteoclast formation through a direct action on osteoclast precursors via peroxisome proliferator-activated receptor gamma 1. *Proc Natl Acad Sci U S A* 98: 2443–2448.

Boolell, M., Allen, M.J., Ballard, S.A., Gepi-Attee, S., Muirhead, G.J., Naylor, A.M. *et al.* (1996) Sildenafil: an orally active type 5 cyclic GMP-specific phosphodiesterase inhibitor for the treatment of penile erectile dysfunction. *Int J Impot Res* 8: 47–52.

Borovikova, L.V., Ivanova, S., Zhang, M., Yang, H., Botchkina, G.I., Watkins, L.R. *et al.* (2000) Vagus nerve stimulation attenuates the systemic inflammatory response to endotoxin. *Nature* 405: 458–462.

de Jonge, W.J., van der Zanden, E.P., The, F.O., Bijlsma, M.F., van Westerloo, D.J., Bennink, R.J. *et al.* (2005) Stimulation of the vagus nerve attenuates macrophage activation by activating the Jak2-STAT3 signaling pathway. *Nat Immunol* 6: 844–851.

Dickson, M. and Gagnon, J.P. (2004) Key factors in the rising cost of new drug discovery and development. *Nat Rev Drug Discov* 3: 417–429.

Gu, R.X., Gu, H., Xie, Z.Y., Wang, J.F., Arias, H.R., Wei, D.Q. *et al.* (2009) Possible drug candidates for Alzheimer's disease deduced from studying their binding interactions with alpha7 nicotinic acetylcholine receptor. *Med Chem* 5: 250–262.

Gutierrez, G.E., Lalka, D., Garrett, I.R., Rossini, G. and Mundy, G.R. (2006) Transdermal application of lovastatin to rats causes profound increases in bone formation and plasma concentrations. *Osteoporos Int* 17: 1033–1042.

Howard, P.A. and Delafontaine, P. (2004) Nonsteroidal anti-Inflammatory drugs and cardiovascular risk. *J Am Coll Cardiol* 43: 519–525.

Keiser, M.J., Setola, V., Irwin, J.J., Laggner, C., Abbas, A.I., Hufeisen, S.J. *et al.* (2009) Predicting new molecular targets for known drugs. *Nature* 462: 175–181.

Kem, W.R. (2000) The brain alpha7 nicotinic receptor may be an important therapeutic target for the treatment of Alzheimer's disease: studies with DMXBA (GTS-21). *Behav Brain Res* 113: 169–181.

Lindstrom, T.M. and Robinson, W.H. (2010) Rheumatoid arthritis: a role for immunosenescence? *J Am Geriatr Soc* 58: 1565–1575.

Maeda, T., Matsunuma, A., Kawane, T. and Horiuchi, N. (2001) Simvastatin promotes osteoblast differentiation and mineralization in MC3T3-E1 cells. *Biochem Biophys Res Commun* 280: 874–877.

Martin, L.F., Kem, W.R. and Freedman, R. (2004) Alpha-7 nicotinic receptor agonists: potential new candidates for the treatment of schizophrenia. *Psychopharmacology (Berl)* 174: 54–64.

Meyer, E.M., Tay, E.T., Papke, R.L., Meyers, C., Huang, G.L. and de Fiebre, C.M. (1997) 3-[2,4-Dimethoxybenzylidene]anabaseine (DMXB) selectively activates rat alpha7 receptors and improves memory-related behaviors in a mecamylamine-sensitive manner. *Brain Res* 768: 49–56.

Mundy, G.R. (2001) Statins and their potential for osteoporosis. *Bone* 29: 495–497.

Olincy, A., Harris, J.G., Johnson, L.L., Pender, V., Kongs, S., Allensworth, D. *et al.* (2006) Proof-of-concept trial of an alpha7 nicotinic agonist in schizophrenia. *Arch Gen Psychiatry* 63: 630–638.

Oxlund, H. and Andreassen, T.T. (2004) Simvastatin treatment partially prevents ovariectomy-induced bone loss while increasing cortical bone formation. *Bone* 34: 609–618.

Oxlund, H., Dalstra, M. and Andreassen, T.T. (2001) Statin given perorally to adult rats increases cancellous bone mass and compressive strength. *Calcif Tissue Int* 69: 299–304.

Pan, X., Yu, X., Qin, L. and Zhang, P. (2010a) *'Old drugs'* for the treatment of rheumatoid arthritis: will the cholinergic anti-inflammatory pathway and anti-nociceptive pathway work? *Inflamm Res* 59: 1005–1007.

Pan, X.H., Zhang, J., Yu, X., Qin, L., Kang, L. and Zhang, P. (2010b) New therapeutic approaches for the treatment of rheumatoid arthritis may rise from the cholinergic anti-inflammatory pathway and antinociceptive pathway. *ScientificWorldJournal* 10: 2248–2253.

Pedersen, T.R., Berg, K., Cook, T.J., Faergeman, O., Haghfelt, T., Kjekshus, J. *et al.* (1996) Safety and tolerability of cholesterol lowering with simvastatin during 5 years in the Scandinavian Simvastatin Survival Study. *Arch Intern Med* 156: 2085–2092.

Qin, G., Mao, H., Zheng, J., Sia, S.F., Liu, Y., Chan, P.L. *et al.* (2009) Phosphoantigen-expanded human gammadelta T cells display potent cytotoxicity against monocyte-derived macrophages infected with human and avian influenza viruses. *J Infect Dis* 200: 858–865.

Ren, W., Blasier, R., Peng, X., Shi, T., Wooley, P.H. and Markel, D. (2009) Effect of oral erythromycin therapy in patients with aseptic loosening of joint prostheses. *Bone* 44: 671–677.

Ren, W., Wu, B., Peng, X., Mayton, L., Yu, D., Ren, J. *et al.* (2006) Erythromycin inhibits wear debris-induced inflammatory osteolysis in a murine model. *J Orthop Res* 24: 280–290.

Rowley, T.J., McKinstry, A., Greenidge, E., Smith, W. and Flood, P. (2010) Antinociceptive and anti-inflammatory effects of choline in a mouse model of postoperative pain. *Br. J Anaesth* 105: 201–207.

Salt, E. and Frazier, S.K. (2010) Adherence to disease-modifying antirheumatic drugs in patients with rheumatoid arthritis: a narrative review of the literature. *Orthop Nurs* 29: 260–275.

Schrader, H., Stovner, L.J., Helde, G., Sand, T. and Bovim, G. (2001) Prophylactic treatment of migraine with angiotensin converting enzyme inhibitor (lisinopril): randomised, placebo controlled, crossover study. *BMJ* 322: 19–22.

Sciulli, M.G., Renda, G., Capone, M.L., Tacconelli, S., Ricciotti, E., Manarini, S. *et al.* (2006) Heterogeneity in the suppression of platelet cyclooxygenase-1 activity by aspirin in coronary heart disease. *Clin Pharmacol Ther* 80: 115–125.

Thylin, M.R., McConnell, J.C., Schmid, M.J., Reckling, R.R., Ojha, J., Bhattacharyya, I. *et al.* (2002) Effects of simvastatin gels on murine calvarial bone. *J Periodontol* 73: 1141–1148.

Tracey, K.J. (2002) The inflammatory reflex. *Nature* 420: 853–859.

Tronvik, E., Stovner, L.J., Helde, G., Sand, T. and Bovim, G. (2003) Prophylactic treatment of migraine with an angiotensin II receptor blocker: a randomized controlled trial. *JAMA* 289: 65–69.

van Maanen, M.A., Stoof, S.P., van der Zanden, E.P., de Jonge, W.J., Janssen, R.A., Fischer, D.F. *et al.* (2009) The alpha7 nicotinic acetylcholine receptor on fibroblast-like synoviocytes and in synovial tissue from rheumatoid arthritis patients: a possible role for a key neurotransmitter in synovial inflammation. *Arthritis Rheum* 60: 1272–1281.

Wang, H., Yu, M., Ochani, M., Amella, C.A., Tanovic, M., Susarla, S. *et al.* (2003) Nicotinic acetylcholine receptor alpha7 subunit is an essential regulator of inflammation. *Nature* 421: 384–388.

Yasuda, O., Takemura, Y., Kawamoto, H. and Rakugi, H. (2008) Aspirin: recent developments. *Cell Mol Life Sci* 65: 354–358.

Yazawa, H., Zimmermann, B., Asami, Y. and Bernimoulin, J.P. (2005) Simvastatin promotes cell metabolism, proliferation, and osteoblastic differentiation in human periodontal ligament cells. *J Periodontol* 76: 295–302.

Yeomans, N.D. (2010) Aspirin: old drug, new uses and challenges*. J Gastroenterol Hepatol, in press.

Zhang, P. and Qin, L. (2010) Potential use of erythromycin to prevent and treat prosthetic failure. *J Clin Pharmacol* 50: 858–860.